with its two aliphatic methyl groups and second de-shielded methyl group. Only one structure is finally allowed: 3,4,4-trimethyl-5-oxo-*trans*-2-hexenoic acid (VIII).

To confirm structure VIII, the acid was synthesized. 3,3-Dimethyl-2,4-pentanedione, b.p. 173° (lit. 173°),[16] giving a single peak on gas–liquid chromatography, was stirred for 24 hr. at room temperature with triethyl phosphonoacetate[17] to give a 71% yield (based on re-covered diketone) of ethyl 3,4,4-trimethyl-5-oxo-*trans*-2-hexenoate (IX), b.p. 76–80° (0.4 mm.), λ_{max} 222 mμ, ϵ 12,600 (*Anal.* Found: C, 66.33; H, 9.00). When this ester was saponified at room temperature with potassium hydroxide in methanol, crystalline compound VIII, m.p. 128–129°, (*Anal.* Found: C, 63.72; H, 8.30) was obtained on acidification. The synthetic acid was identical with the natural acid in ultraviolet, infra-red, n.m.r. and mass spectra; a mixture melting point was undepressed.

Extraction of the mother liquors with ether yielded two isomers of VIII: 4,4-dimethyl-3-methylene-5-oxo-hexanoic acid (X), m.p. 53° (*Anal.* Found: C, 63.52; H, 8.26), whose n.m.r. spectrum contained olefinic protons at τ 4.75 and τ 4.70 and a singlet methylene at τ 7.00, but only 1 deshielded methyl, at τ 7.89, together with the two aliphatic methyls at τ 8.75; and a very small amount of the sterically less favorable 3,4,4-trimethyl-5-oxo-*cis*-2-hexenoic acid, existing predominantly as the δ-lactol XI, m.p. 152–154°, λ_{max} 222 mμ (ϵ 10,400), infrared band at 1710 cm.$^{-1}$, whose n.m.r. spectrum indicates an olefinic proton at τ 4.20, an olefinic methyl's broad singlet at τ 8.04, a lactol methyl singlet at τ 8.41, and a six-proton singlet at τ 8.83.

The mass spectra of the isomeric acids are of interest. That of VIII has its highest mass peak at m/e 128 (M − 42), and that of its ethyl ester (IX) shows only a very small molecular ion peak at m/e 198, but a very intense peak at m/e 156 (M − 42). Apparently, the molecular ions from VIII and IX both lose ketene (42 m.u.) rapidly from C-5 and C-6, suggesting the novel fragmentation shown. The mass spectrum of the isomeric acid XI,


M
m/e 170 (R = H, VIII)
m/e 198 (R = C$_2$H$_5$, IX)

M − 42
m/e 128 (R = H)
m/e 156 (R = C$_2$H$_5$)
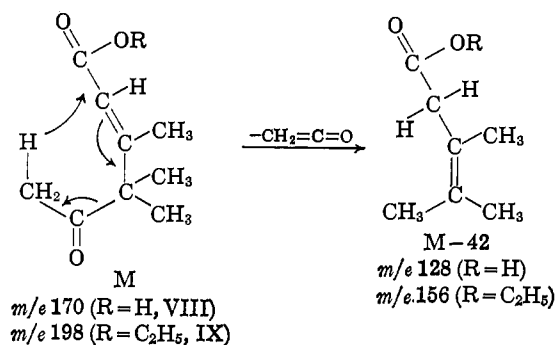
existing predominantly in the δ-lactol form shown, con-tains neither a molecular ion nor an ion at M − 42. This isomer fragments by initial loss of water, followed by loss of ketene, to give peaks at m/e 152 (M − 18) and m/e 110 (M − 60), respectively. This sequence is readily ex-plained by the fragmentations shown.

Among the mass spectra of the isomers, only that of X contains a molecular ion peak at m/e 170; fragmen-

(16) M. F. Ansell, W. J. Hickinbottom, and A. A. Hyatt, *J. Chem. Soc.*, 1592 (1955).

(17) G. M. Kosolapoff, "Organophosphorus Compounds," 1st ed, John Wiley and Sons, Inc., New York, N. Y., 1950, Chapter 7.

XI
m/e 170

m/e 152

m/e 110
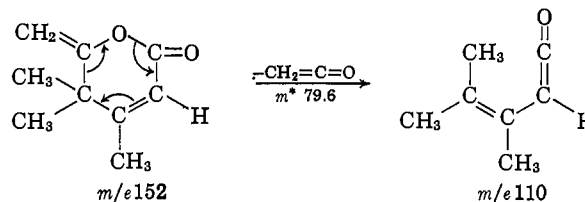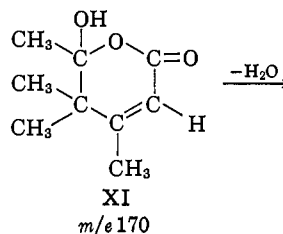
tation occurs along several pathways, but loss of ketene is minor.

The reactions from IV to VIII have not been docu-mented by study of their enzymatic catalysis by ex-tracts from camphor-grown cells. The suggested con-version of IV to V is analogous to the Baeyer–Villiger oxidation of ketones with peracids,[18] the enzymatically documented biological reactions in steroid[19] and cam-phor[20] oxidation by microorganisms, and the accumu-lation of fencholides[10] by the strain T$_1$ used in these studies. Additional support for the proposed mecha-nism derives from the presence of an enzyme which cata-lyzes the rapid oxidation of DPNH in the presence of isoketocamphoric acid (VII).[11] Thus, it may be in-ferred that isohydroxycamphoric acid (VI) and its lactone (V) are intermediates. The conversion of isoketocam-phoric acid (VII) to hexenoic acid VIII is analogous to the sequence mevalonic acid 5-pyrophosphate → di-methylallyl pyrophosphate,[21,22] and to the isoprenoid degradation.[23]

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(20) H. E. Conrad, R. DuBus, and I. C. Gunsalus, *Biochem. Biophys. Res. Commun.*, 6, 293 (1961).

(21) F. Lynen, H. Eggerer, U. Henning, and I. Kessel, *Angew. Chem.*, 70, 738 (1958).

(22) B. W. Agranoff, H. Eggerer, U. Henning, and F. Lynen, *J. Biol. Chem.*, 235, 326 (1960).

(23) W. Seubert and E. Fass, *Biochem. Z.*, 341, 35 (1964).

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Valence Isomerization of a *cis*-Dienone to an α-Pyran

Sir:

The valence isomerization between *cis*-dienones and α-pyrans has been invoked in several instances[1] to

(1) (a) G. Büchi and N. C. Yang, *J. Am. Chem. Soc.*, 79, 2318 (1957); (b) A. T. Balaban, G. Makai, and C. D. Nenitzescu, *Tetrahedron*, 18, 257 (1962); (c) A. Hinnen, J. Dreux, and M. Delépine, *Compt. Rend.*, 255, 1747 (1962); (d) J. C. Anderson, D. G. Lindsay, and C. B. Reese, *Tetrahedron*, 20, 2091 (1964); (e) S. Sarel and J. Rivlin, *Israel J. Chem.*, 1, 221 (1963); (f) S. Sarel and J. Rivlin, *Tetrahedron Letters*, 821 (1965).
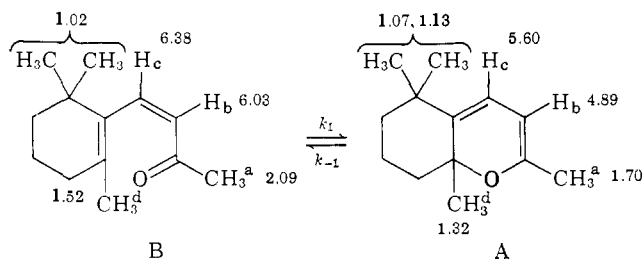
Figure 1. Nmr spectral data for cis-β-ionone and the corresponding α-pyran.

explain certain otherwise enigmatic results. We wish to report the first clear-cut example of such a valence isomerization. A sample of 1-oxa-2,5,5,9-tetramethyl-1,5,6,7,8,10-hexahydronaphthalene (A) was obtained by irradiation of trans-β-ionone according to the procedure of Büchi and Yang.[1a] As Figure 1 shows, the nmr spectrum of A is in complete accord with the α-pyran structure assigned this substance by Büchi and Yang. However, there appeared in the spectrum, in addition to the bands attributed to the α-pyran, the following series of weak bands: singlet at δ 1.02 another at 2.09, and a modified AB pattern at 6.03 and 6.38 (J_{AB} = 12.5 cps). Two features of these extraneous bands were striking. They were not removed by further purification of the pyran, and they were a part of the series of bands expected for the unknown cis-β-ionone (B).

If cis-β-ionone were responsible for these bands and were also in mobile equilibrium with the α-pyran, it seemed reasonable to expect the equilibrium content of the less stable isomer to be increased with increasing temperature. The predicted change can indeed be observed; the spectrum of B (Figure 1) shows an increase in intensity with a compensating decrease in that due to A as the temperature of the nmr probe is increased. The total spectrum reverts to its original form when the temperature is returned to normal. This process has been repeated a number of times with a single sample with no apparent decomposition. On the basis of the nmr spectrum, and the complete reversibility of the process, we have assigned B the cis-β-ionone structure.

Since the AB patterns for the C-3 and C-4 protons in A and B are separated cleanly from each other and from all other bands in the spectrum, the equilibrium constant for the valence isomerization can be measured conveniently. At 327°K it is 4.61 and at 386°K it is 1.52. The α-pyran is more stable than cis-β-ionone, $\Delta H°$ = 5.5 kcal/mole, but the thermodynamic stability is largely compensated by the entropy change (−14 eu) in going from the monocyclic to the bicyclic molecule. The rigidity of the bicyclic α-pyran is reflected in the separate resonance peaks for the two methyls of the geminal methyl grouping.

The rate of the valence isomerization was determined by perturbing the equilibrium and measuring the rate of reversion. An nmr tube containing 150 mg of the pyran in 500 mg of tetrachloroethylene was heated to 120° for 10 min and quenched in a Dry Ice bath. The tube was then placed in the probe and allowed to reach thermal equilibrium. The rate was followed by measuring the decrease in the peak height of the larger peak in the doublet at δ 6.03. Using the rate equation

$$2.3 \log \frac{x_0 - x_e}{x_t - x_e} = (k_1 + k_{-1})t$$

where x = peak height,[2] and values of the equilibrium constant calculated from the data obtained at higher temperatures, both k_1 and k_{-1} were obtained. At 18° k_1 = 1.4 × 10⁻³ sec⁻¹ while k_{-1} = 1.3 × 10⁻⁴ sec⁻¹. Measurements at several temperatures between 0 and 18° gave E_a = 20 kcal/mole for the cis-dienone to α-pyran reaction and E_a = 27 kcal/mole for the reverse process.

The magnitude of the rate difference for the valence isomerization of the cis-dienone to pyran compared with that of cis-2-cis-4-trans-6-octatriene to trans-5,6-dimethyl-1,3-cyclohexadiene[3] seems surprisingly large. A factor of between five and six powers of ten can be estimated from the reported data. In view of the high rate of the dienone to pyran isomerization the failure of previous investigators[1] to isolate both valence isomers seems reasonable.[4]

(2) A. A. Frost and R. G. Pearson, "Kinetics and Mechanisms of Homogeneous Chemical Reactions," John Wiley and Sons, Inc., New York, N. Y., 2nd ed, 1961, p 186.

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(4) We are pleased to acknowledge the generous support provided for this work by the National Science Foundation through Grants G-23702 and GP 4985. Financial assistance from the National Science Foundation for the purchase of the Varian A-60 nmr spectrometer used in this study is also gratefully acknowledged.

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The Conformational Preference of the Nonbonding Electron Pair in Piperidine

Sir:

Central to the problem of the spatial requirements of nonbonding electrons has been the determination of the conformational preference of the nitrogen lone pair in piperidine. Aroney and LeFèvre[1] reported that the sign and magnitude of the molar Kerr constants of piperidine and N-methylpiperidine require the electron lone pair to be larger[2] than hydrogen, and, in fact, approximately equivalent in size to the methyl group. These conclusions have been criticized by several groups.[3-5] Thus, Allinger and co-workers[5] have presented arguments that the methyl group is considerably larger,[2] and hydrogen somewhat larger, than the lone pair. From the low-temperature nmr spectra of N-substituted and unsubstituted piperidines, we have obtained evidence which corroborates portions of the conclusions of both groups. Our evidence indicates that the lone pair in N-substituted piperidines is indeed axially oriented,[5] but that the

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